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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/748,233	MARTUZA ET AL.	
	Examiner	Art Unit	
	Wu-Cheng Winston Shen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response received on 11/05/2007 has been entered. Claims 1-6 were cancelled. Claim 7 is amended. Claims 7-18 are pending and currently under examination.

This application 10/748,233 filed on 12/31/2003 is a divisional of Ser. No. 09/625,509, filed July 25, 2000, now U.S. Pat. No. 6,699,468, which is a divisional of Ser. No. 09/004,511, filed Jan. 8, 1998, which is a continuation of U.S. patent application Ser. No. 08/478,800, filed Jun. 7, 1995, now abandoned, which is a continuation of U.S. Ser. No. 08/264,581 filed Jun. 23, 1994, now U.S. Pat. No. 5,585,096.

Claim Objection

1. Claims 7-18 are objected to because of the following informalities: Claim 7 in line 3 should read "and *in* the ribonucleotide reductase gene" or "in each of the γ34.5 and ribonucleotide reductase genes" so that the claim clearly indicates that the gene is altered and that "and the ribonucleotide reductase gene" does not appear to be an incomplete and independent phrase. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Previous rejection of claims 7-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention, is ***withdrawn*** because claim 7 has been amended and claims 8-18 depend from claim 7.

Claim 7 is amended and no longer recites the phrase "relative to wild type". Claim 8-18 depend from claim 7.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (c) or 1.321 (d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

3. Previous rejection of claims 7-18 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 2 of U. S. Patent number 5,585,096, issued on 12/17/1996, is ***withdrawn*** because a terminal disclaimer has been filed on 11/05/2007, and approved on 11/26/2007.

Claim Rejection - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 7-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a herpes simplex virus with a genome (i) that comprises an expressible non-herpes simplex virus nucleotide sequence encoding a cytokine capable of eliciting an immune response in a tumor cell and (ii) that is altered in the γ34.5 gene and in the ribonucleotide reductase gene such that no functional γ34.5 gene or ribonucleotide reductase gene product is made, wherein the neurovirulence of said herpes simplex virus is attenuated and said herpes simplex virus and is capable of replication in dividing cells, but not in non-dividing cells, **does not** reasonably provide enablement for a herpes simplex virus with a genome comprising 1) any alteration in the γ34.5 or ribonucleotide reductase genes other than an alteration that results in a lack of function of each gene product, or 2) for a viral particle exhibiting any effect from the alteration other than attenuation of neurovirulence and the effect

of having the ability to replicate in dividing cells and not in non-dividing cells, or 3) for a HSV viral vector comprising expressible non-herpes simplex virus nucleotide sequence encoding *any* desired protein for eliciting an immune response in a tumor cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The basis of this scope of enablement rejection is hinged on (1) the breadth encompassed by the limitation "that is *altered* in the γ34.5 gene and the ribonucleotide reductase gene" recited in claim 7, and (2) the intended use of the herpes simplex viral vector capable of selectively killing human tumor cells *in vivo*.

The nature of the instant invention is a herpes simplex virus with a genome (i) that comprises an expressible non-herpes simplex virus nucleotide sequence encoding a desired protein capable of eliciting an immune response in a tumor cell, and (ii) that is mutated in the γ34.5 gene and the ribonucleotide reductase genes, wherein the mutations in the γ34.5 gene and the ribonucleotide reductase gene results in a lack of function of the γ34.5 gene product and the ribonucleotide reductase, and allows the herpes simplex virus to replicate in dividing cells, but not in non-dividing cells.

The breadth of the claim 1 reads on any alteration in the γ34.5 gene and the ribonucleotide reductase gene, including, for instance, a silent or other mutation in the γ34.5 gene and the ribonucleotide reductase gene at nucleotide level that does not result in a total lack of functional gene products.

The specification discloses the following information in the indicated paragraphs:

[0034] Viruses of the instant invention are engineered to contain alterations in the expression of at least two specific HSV-1 genes: (1) the .gamma.34.5 gene and (2) the ribonucleotide reductase gene. Alterations in this regard include any that disrupt the expression of the product of both of the γ34.5 gene and the ribonucleotide reductase gene. The presence of such multiple mutations further reduces the possibility of reversion to wild-type pathogenicity.

[0036] Initial work on the use of attenuated herpes simplex virus vectors for use in anti-tumor therapy employed HSV-1 mutated in one gene allowing the vector to replicate in dividing cells, but not in non-dividing cells. Two such single gene-mutant herpes simplex virus vectors are (1) hrR3, deficient in ribonucleotide reductase, containing an Escherichia coli lacZ gene insertion in the ICP6 gene that encodes the large subunit of RR, [Mineta, T. et al., Gene Therapy 1:S78 (1994) and Mineta et al., J. Neurosurg. 80: 381 (1994)]; and (2)

R3616, which contains mutations in both copies of the γ34.5 gene. Markert et al., Neurosurgery 32: 597 (1993).

[0038] Herpes simplex virus ribonucleotide reductase is required for efficient viral growth in non-dividing cells but not in many dividing cells.

[0042] Herpes simplex virus mutants deficient in only the γ34.5 gene, such as R3616, are attenuated for neurovirulence, which reduces the possible damage to normal brain cells. Goodman et al., J. Virol. 63: 1153 (1989); Chou et al., Science 250: 1262 (1990).

The specification does not disclose any alteration in the herpes simplex virus ribonucleotide reductase other than insertion of LacZ in the ICP6 gene, and the specification does not disclose any alteration in the herpes simplex virus γ34.5 gene other than mutations that disrupt the function of γ34.5 gene (also known as ICP34.5 gene) (See Figure 2 of instant application).

In the art, it has been shown that variants ICP34.5 causes neuronvirulence. For instance, **Bower et al.** teach that two intra-strain variants of herpes simplex virus type 1 (HSV-1) were isolated from a newborn with fatal disseminated infection. A small-plaque-producing variant (SP7) was the predominant virus (>99%) in the brain, and a large-plaque-producing variant (LP5) was the predominant virus (>99%) in the lung and gastrointestinal tract. PCR analysis using primers from within the ICP34.5 gene indicated differences for SP7, LP5, and KOS. Sequencing data indicated two sets of deletions in the UL34.5 gene that distinguish SP7 from LP5. Both SP7 and LP5 variants were neurovirulent (lethal following intracranial inoculation of young BALB/c mice) (See abstract, and Figures 7 and 8, pages 3848 and 3849, Bower et al.

Intra-strain variants of herpes simplex virus type 1 isolated from a neonate with fatal disseminated infection differ in the ICP34.5 gene, glycoprotein processing, and neuroinvasiveness, *J Virol.* 73(5):3843-53, 1999).

With regard to alteration in HSV ribonucleotide reductase gene, **Salvucci et al.** reported polymorphism within the herpes simplex virus (HSV) ribonucleotide reductase large subunit (ICP6) and the viruses harboring the variant ICP6 gene can infect and grow in non-tumor cells, including fibroblasts (See abstract, and Figure 6, page 1128, Salvucci et al., Polymorphism within the herpes simplex virus (HSV) ribonucleotide reductase large subunit (ICP6) confers type specificity for recognition by HSV type 1-specific cytotoxic T lymphocytes, *J Virol.* 69(2):1122-31, 1995).

Therefore, the status of art indicates lack of predictability in terms of (i) whether any alteration other than a null mutation in γ34.5 will attenuate neurovirulence of a herpes simplex virus, (ii) whether any alteration other than a null mutation in ribonucleotide reductase will render the virus to selectively infect and replicate in fast dividing tumor cells, but not in non-dividing cells. It is worth noting again that the breadth of the claim 1 reads on any alteration in the γ34.5 gene and the ribonucleotide reductase gene, including a silent mutation in the γ34.5 gene and the ribonucleotide reductase gene at nucleotide level that does not affect expression of functional gene products as well as mutations that merely alter or reduce activity of the gene products.

Regarding a viral particle exhibiting any effect from the alteration other than attenuation of neurovirulence and the effect of having the ability to replicate in dividing cells and not in non-dividing cells, being considered not enabled, the Examiner notes that it is unpredictable what

activity the virus will have with anything other than a total lack of function of the two genes. One of skill in the art would not know how to *use* the claimed virus exhibiting any effect of altering the two genes other than the neurovirulence of said herpes simplex virus is attenuated and said herpes simplex virus and is capable of replication in dividing cells, but not in non-dividing cells. It is worth emphasizing that the full breadth of "alteration" recited in the claim reads on any change in each one of the γ34.5 gene and the ribonucleotide reductase gene. Relevant to this unpredictability issue in terms of connection between a genetic mutation and a resulting phenotype, it is noted, as recently reviewed by **Parmley et al.**, 2007, that even silent SNPs encoding the same amino acid residues are not necessarily neutral with regard to their effects on the functions of polypeptides, and there are two additional mechanisms affecting the function of a given polypeptide: (1) modification of protein structure and activity, mediated by induction of translational pausing during co-translational protein folding, and (2) modification of protein abundance mediated by alteration in mRNA stability via changed secondary structures of mRNA, which in turn leads to perturbation in protein synthesis (See abstract, Parmley et al., How do synonymous mutations affect fitness? *Bioessays*, 29(6): 515-9, 2007). In other words, alterations in either protein folding or translational efficiency result on changed protein functions encoded by synonymous mutations.

It is noted that the specification discloses LacZ is used to disrupt ICP34.5 gene (i.e. γ34.5 gene) (See Figure 1), and the specification also discloses a HSV contains an expressible non-herpes simplex virus nucleotide sequence encoding a desired protein capable of eliciting an immune response in the subject (See paragraph [0024]). The specification discloses that the mutant herpes simplex virus vector of the invention can be further altered to express cytokines,

the limitation of claim 8, in the tumor target cell in order to elicit an immune response against the tumor cells. For example, a mutant herpes simplex virus vector can induce viral-mediated killing of tumor cells, which then is amplified by a cytokine-enhanced immune response, a cytokine having been expressed by the vector itself (See paragraph [0077]). However, the specification does not provide any support that the expression of LacZ, the limitation of claim 9, would elicit an immune response in the subject.

In view of the state of the art, the unpredictability in the art, and the lack of specific guidance and working examples in the specification, one of skill in the art would have to perform undue experimentation to make and use the claimed invention as recited in claims 7-18.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 7, 9-13, 17 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roizman et al. (U.S. patent No. 6,172,047, issued Jan. 9, 2001; priority date 03/31/1992) taken with Chang et al. (Chang et al., A gene delivery/recall system for neurons which utilizes ribonucleotide reductase-negative herpes simplex viruses, *Virology*, 185(1):437-40, 1991).

Claim interpretation: It is noted that in the art G207, as recited in claim 10 of instant application, is the name of an HSV that contains deletions of both copies of the γ34.5 gene as

well as a LacZ insertion in the ICP6 gene, which is the large subunit (ICP6) of ribonucleotide reductase (RR).

Roizman et al. teaches the following: **(i)** The function of the gene γ34.5 in its ability to enable the virus to replicate, multiply and spread in the central nervous system (CNS) was demonstrated by a set of recombinant viruses and by testing their abilities to cause fatal encephalitis in the mouse brain. The mutant viruses lacking the gene therefore lost their ability to multiply and spread in the CNS and eyes and therefore are non-pathogenic. See Chou et al., Science, 250: 1212-1266, 1990 (See lines 35-42, col. 4, Roizman et al., 2001). **(ii)** The use of the HSV-1 virus with a specific mutation in the γ34.5 gene provides a method of therapeutic treatment of tumorogenic diseases both in the *CNS and in all other parts of the body.* The "γ34.5 minus" virus can induce apoptosis and thereby cause the death of the host cell, but this virus cannot replicate and spread. Therefore, given the ability to target tumors within the CNS, the γ34.5 minus virus has proven a powerful therapeutic agent for hitherto virtually untreatable forms of CNS cancer (See bridging paragraph, col. 5-6, Roizman et al., 2001). Roizman et al. further teaches that the γ34.5 gene placed under a suitable target specific promoter (which reads on claims 13 and 17 of instant application) would be expressed, thus inducing an anti-apoptotic effect in the neuron without the potential for stress induced neurovirulence (See lines 44-46, 56-60 col. 6, Roizman et al., 2001).

However, Roizman et al., do not teach a herpes simplex virus with a genome that comprises alteration in the ribonucleotide reductase (RR) gene.

At the time of filing of instant application, a herpes simplex virus with a genome that is altered in the ribonucleotide reductase gene is known in the art. For instance, Chang et al.

teaches that herpes simplex virus type-1 (HSV-1) is able to infect both non-neuronal and neuronal cells (See introduction, Chang et al., 1991). Chang et al. also teaches that ribonucleotide reductase (RR)-negative herpes simplex virus type-1 (HSV-1) is a useful vector for gene delivery into neuronal cells. Chang et al. used hrR3, a genetically engineered HSV-1 mutant which has an in-frame insertion of the bacterial lacZ gene into the HSV gene that encodes the large subunit (ICP6) of ribonucleotide reductase (RR), resulting in the ICP6::lacZ chimeric gene. Chang et al reported that the infection was performed in the presence of acyclovir, hrR3 appeared to become "latent". Chang et al. further teaches that the introduction of *a foreign gene* into neuronal cells by a RR-negative herpes simplex virus, and the subsequent induction of gene expression by another non-complementing virus, may constitute a prototype gene delivery/recall system for neurons (See abstract, Chang et al., 1991). Chang et al further teaches that ribonucleotide reductase (RR)-negative herpes simplex virus type-1 (HSV-1) grows in actively dividing cells, but the growth is severely impaired in growth arrested, non-dividing cells (See bridging paragraph, pages 437-438, Chang et al., 1991).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to combine the characteristics of a mutant herpes simplex virus comprising a disrupted γ34.5 herpes simplex, which is non-pathogenic and has lost the ability of to multiply and spread in the CNS and in all other parts of the body, as taught by Roizman et al. 2001, with the characteristics of a RR-negative herpes simplex virus that can grow in actively dividing cells, but the growth is severely impaired in growth arrested, non-dividing cells, as taught by Chang et al. 1991.

It would have been obvious at the time of filing to combine the teachings of Roizman et al. 2001 with the teachings of Chang et al. 1991, to arrive at the claimed herpes simplex viruses as recited in claims 7, 9, 11, 12, 17 and 18 of instant application.

One having ordinary skill in the art would have been motivated to combine the teachings of Roizman et al. 2001 with the teachings of Chang et al. 1991 because the disrupted γ34.5 gene renders the HSV vector non-pathogenic and the disrupted ribonucleotide reductase gene render the HSV vector specific targeting to fast dividing tumor cells without harming healthy cells, for the treatment of CNS or non-CNS cancers. Combination of the mutations would result in a non-pathogenic vector, as taught by Roizman et al., 2001 (See last paragraph, col.5), that targets specifically fast dividing tumor cells, as taught by Chang et al., 1991, which indicates the disruption of ICP6, either by LacZ insertion in the ICP6:LacZ strain or by deletion in the ICP6Δ strain, results in severe growth impairment in non-dividing cells (See first paragraph, left column, page 438).

There would have been a reasonable expectation of success given (1) the demonstration that the "γ34.5 minus" virus can induce apoptosis and thereby cause the death of the host cell, but this virus cannot replicate and spread, by the teachings of Roizman et al., 2001, and (2) the demonstration that ribonucleotide reductase (RR)-negative herpes simplex virus type-1 (HSV-1) vector for introduction of a foreign gene can grow in actively dividing cells, but the growth is severely impaired in growth arrested, non-dividing cells, by the teachings of Chang et al., 1991

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

6. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Roizman et al. (U.S. patent No. 6,172,047, issued Jan. 9, 2001; priority date 03/31/1992) taken with Chang et al. (Chang et al., A gene delivery/recall system for neurons which utilizes ribonucleotide reductase-negative herpes simplex viruses, *Virology*, 185(1):437-40, 1991) as applied to claim 7 above, and further in view of Vile et al. (Vile RG and Hart IR, Targeting of cytokine gene expression to malignant melanoma cells using tissue specific promoter sequences. *Ann Oncol.* 5 Suppl 4:59-65, 1994).

The teachings of Roizman and Chang et al. have been discussed in the preceding rejection of claims 7, 9-13, 17 and 18 under 35 U.S.C. 103(a) as being unpatentable over Roizman et al. 2001 taken with Chang et al. 1991.

However, the combined teachings of Roizman et al. and Chang et al., do not teach a herpes simplex virus with a genome that expresses an exogenous cytokine gene in the context of cancer development and treatment as required by claim 8.

At the time of filing of instant application, transduction of tumor cells in vitro with cDNAs encoding various cytokines and/or immune accessory molecules has been shown to diminish or eliminate tumorigenicity when such cells are returned in vivo to syngeneic animals. For instance, Vile et al. teaches using the 5' flanking region of the murine tyrosinase gene to direct expression of three different cytokine genes [murine interleukin 2 (IL-2), IL-4 and macrophage colony-stimulating factor (M-CSF)] specifically to murine melanoma cells (See abstract, Vile et al. *Ann Oncol.* 5 Suppl 4:59-65, 1994).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to exogenously express a cytokine gene in melanoma, by the

teaching of Vile et al., 1994, in the herpes simplex virus vector with disrupted both γ34.5 and ribonucleotide reductase gene that exhibits no neurovirulence and specifically targeting to fast dividing cancer cells, by the combined teachings of Roizman et al., 2001 and Chang et al., 1991.

It would have been obvious at the time of filing to combine the teachings of Roizman et al. 2001 and Chang et al. 1991 on a HSV vector for cancer treatment and the exogenous expression of cytokine in treating melanoma, to arrive at the claimed herpes simplex viruses recited in claims 7 and 8 of instant application.

One having ordinary skill in the art would have been motivated to utilize the HSV vector that exhibits characteristics favorable gene transfer, by combined teachings of Roizman 2001 and Chang 1999, to introduce an exogenous cytokine gene into a tumor cell, by the teachings of Vile et al.,1994, becasue the HSV vector being non-pathogenic and specifically targeting to fast dividing tumor cells without harming healthy cells, and the exogenous expression of a cytokine gene results in diminishing or eliminating tumorigenicity. One of skill in the art would have been motivated to combine the two mutations because combination of the mutations would result in a non-pathogenic vector, as taught by Roizman et al., 2001 (See last paragraph, col.5), that targets specifically fast dividing tumor cells, as taught by Chang et al., 1991, which indicates the disruption of ICP6, either by LacZ insertion in the ICP6:LacZ strain or by deletion in the ICP6Δ strain, results in severe growth impairment in non-dividing cells (See first paragraph, left column, page 438).

There would have been a reasonable expectation of success given (1) the characteristics of an HSV vector by the combined teachings of Roizman et al. and Chang et al. being non-

pathogenic and specifically targeting to fast dividing tumor cells , (2) the demonstrateion of exogenous expression of IL-2 coding sequences driven by a tissue specific promoter via direct injection in the murine melanoma cells completely abrogated their tumorigenicity in syngeneic mice, by the teachings of Vile et al., 1994.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

7. Claim 14-16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Roizman et al. (U.S. patent No. 6,172,047, issued Jan. 9, 2001; priority date 03/31/1992) taken with Chang et al. (Chang et al., A gene delivery/recall system for neurons which utilizes ribonucleotide reductase-negative herpes simplex viruses, *Virology*, 185(1):437-40, 1991) as applied to claim 13 above, and further in view of McKay et al. (WO 92/14821, publication date 09/03/1992, PCT/US92/01375, priority date 02/22/1991), and Wright, Jr. (US 5,639,656, issued Jun. 17, 1997, filed 03/31/1994).

The teachings of Roizman and Chang et al. have been discussed in the preceding rejection of claims 7, 9-13, 17 and 18 under 35 U.S.C. 103(a) as being unpatentable over Roizman et al. 2001 taken with Chang et al. 1991.

However, the combined teachings of Roizman et al. and Chang et al., do not teach a herpes simplex virus with a genome that expresses a exogenous gene, targeting to a specific tumor type with a tumore cell specific promoter, wherein said promoter being nestin promoter, basic fibroblast growth factor (bFGF) promoter, epidermal growth factor (EGF) promoter, as recited in claims 14-16 of instant application.

At the time of filing of instant application, it is known in the art that the expression of certain growth factor genes including bFGF, EGF, nestin genes can serve as markers for detection of various cancers, indicating the promoters of these growth factors being tumor specific with respect to its regulation. For instance, McKay et al. teaches that nestin expression as an indicator of neuroepithelial brain tumors, indicating the nestin promoter being tumor specific with respect to its regulation (See title and abstract, WO 92/14821, publication date 09/03/1992). Wright, 1997 teaches the expression of bFGF, EGF can be used as biological markers of prostate cancer (CaP) or benign prostate hyperplasia (BPH) (See title and lines 30-36. column 2, Wright et al., 1997).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to exogenously express a non-HSV nucleotide sequences encoding a tumor specific marker under the control of the tumor specific promoters of nestin or bFGF, or EGF, by the teaching of Wright or McKay et al., in the herpes simplex virus vector with disrupted both γ34.5 and ribonucleotide reductase gene that exhibits no neurovirulence and specifically targeting to fast dividing cancer cells, by the combined teachings of Roizman et al., 2001 and Chang et al., 1991.

It would have been obvious at the time of filing to combine the teachings of Roizman et al. 2001 and Chang et al. 1991 on a HSV vector for cancer treatment with the expression of a non-HSV nucleotide sequences encoding a tumor specific marker under the control of the tumor specific promoters of nestin or bFGF, or EGF, by the teaching of Wright or McKay et al., to arrive at the claimed herpes simplex viruses as recited in claims 14-16 of instant application.

One having ordinary skill in the art would have been motivated to utilize the HSV vector that exhibits characteristics favorable gene transfer, by combined teachings of Roizman 2001 and Chang 1999, to introduce the expression of a non-HSV nucleotide sequences encoding a tumor specific marker under the control of the tumor specific promoters of nestin or bFGF, or EGF, by the teaching of Wright or McKay et al., becasue the HSV vector being non-pathogenic and specifically targeting to fast dividing tumor cells without harming healthy cells, and the non-HSV nucleotide sequences only express the tumor specific marker in tumor cells. Combination of the mutations would result in a non-pathogenic vector, as taught by Roizman et al., 2001 (See last paragraph, col.5), that targets specifically fast dividing tumor cells, as taught by Chang et al., 1991, which indicates the disruption of ICP6, either by LacZ insertion in the ICP6:LacZ strain or by deletion in the ICP6Δ strain, results in severe growth impairment in non-dividing cells (See first paragraph, left column, page 438).

There would have been a reasonable expectation of success given (1) the characteristics of an HSV vector by the combined teachings of Roizman et al. and Chang et al. being non-pathogenic and specifically targeting to fast dividing tumor cells, (2) the demonstration of nextin expression in a brain tumor specific manner by the teachings of McKay et al, and the expression of bFGF and EGF in a prostate cancer specific manner by the teachings of Wright.

Thus, the claimed invention as a whole was clearly *prima facie* obvious.

Conclusion

8. No claim is allowed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent examiner, Peter Paras, can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

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